REMARKS

After entry of this amendment, claims 31-34, 36-52, 67-73 will be pending in the application. Claims 31 and 67 have been amended to more particularly point out and distinctly claim that which Applicant regards as the invention. The amendments are fully supported by the specification as originally filed and, as such no new matter has been added. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

Claims 67-73, which cover a method for administering a hydrophobic pharmaceutical substance to a patient, were erroneously withdrawn from consideration as being directed to a non-elected invention. Applicants respectfully direct the Examiner's attention to the Office Communication, mailed on February 26, 2004, in which the Examiner required a restriction under 35 U.S.C. § 121 to one of five separate inventions. In a response dated June 28, 2004, the Applicants elected the invention of Group III, in which claims are drawn to a method of administering a macromolecular and/or hydrophobic pharmaceutical substance to a patient. Applicants respectfully point out that the present claims fall within the scope of the elected invention because claims 31-52 were amended to claim a method for administering a macromolecular pharmaceutical substance and claims 67-73 were added to separately claim a method for administering a hydrophobic pharmaceutical substance. Thus, Applicants submit that the Examiner has erroneously contended that claims 67-73 are directed to a non-elected invention and these claims should not be withdrawn from consideration.

1. THE CLAIMS ARE NOT ANTICIPATED

Claims 31 and 32 are rejected under 35 U.S.C. § 102(b) as anticipated by Gross *et al.* (U.S. Patent No. 5,848,991). The Examiner contends that Gross inherently anticipates the claimed invention. For reasons detailed below, these rejections are erroneous and should be withdrawn.

The Examiner erroneously interprets Gross as disclosing the delivery of drugs to the intradermal compartment of a human subject's skin using a single needle with an outlet at a depth of 250 microns to 2 mm, and concludes that practicing Gross would inherently result in a pharmacokinetic profile (PK) similar to subcutaneous injection, but with a higher C_{max} and AUC. Even if the Examiner's contention were correct, Gross would still not anticipate the claims. The claimed PK profile does not require a higher C_{max} and AUC -- instead, the claims require a higher C_{max} and a shorter T_{max} as compared to subcutaneous delivery. There is absolutely no proof in this record that practicing Gross would inherently achieve the PK profile required by the claims.

By way of background, pharmacokinetics (PK) describes the concentration-time history of a drug in the body, and is typically represented graphically by plotting the concentration of the drug in the circulation over time, as shown below.

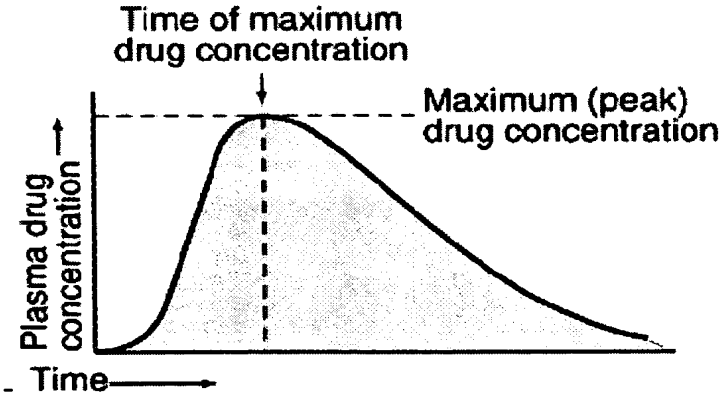

FIG. 1. Representative plasma concentration-time relationship after a single oral dose of a hypothetical drug. Area under the plasma concentration-time curve is indicated by shading. (Reproduced from Merck Manual of Diagnosis and Therapy, 1999, Clinical Pharmacology, reference CK of record).

At least three parameters are typically used to characterize the PK for delivery of a drug -- T_{max}, $C_{max,}$ and AUC. T_{max} is the time required for the drug to reach a maximum serum concentration; C_{max} is the maximum (or peak) serum concentration of the drug reached within a given dose and route of administration; whereas the area under the serum concentration curve ("AUC") is a measure of bioavailability. The claims of the present invention require a higher C_{max} and a shorter T_{max} compared to subcutaneous administration; *e.g.,* claims 31 and 67.

While there is absolutely no evidence that practicing Gross would inherently result in the claimed PK profile, assuming *arguendo* Gross were used to inject a drug into the intradermal space, the claimed PK profile would *not inevitably* result. Mere injection of a drug into the intradermal compartment does not inevitably result in a higher C_{max} and shorter T_{max} as compared to subcutaneous delivery. In this regard, the Examiner's attention is invited to experimental controls presented in the specification, and the Declaration by Dr. Ronald J. Pettis under 37 C.F.R. §1.132, submitted in connection with parent application no. 09/606,909 ("the Pettis Declaration"), a copy of which is attached herewith for the Examiner's convenience. The present specification describes examples where delivery of a substance to the intradermal compartment results in a nearly identical pharmacokinetic profile as compared to subcutaneous delivery. In particular, when long acting insulin was administered to the intradermal compartment, as described in Example V of the instant specification, similar PK profiles were obtained relative to subcutaneous delivery (See ¶ [0069] of the instant application as published). Furthermore, the Pettis Declaration shows that mere injection of a drug to the intradermal compartment does *not inevitably* result in a higher C_{max} and shorter T_{max} as compared to subcutaneous delivery. As demonstrated by the Pettis Declaration, delivery of substances to the intradermal space can result in an increased C_{max} and an increased AUC (*see* Pettis Decl., ¶ 9). However, in those same examples, the

T_{max} attained via intradermal delivery was not significantly different from the T_{max} attained via subcutaneous delivery (*see* Exhibit B attached to the Pettis Declaration).

In order for a prior art reference to inherently anticipate the claimed invention, the method disclosed must *inevitably* result in the claimed invention, *i.e.*, the claimed PK profile must be achieved *each time and every time* the methods of Gross are practiced. *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323 (C.C.P.A. 1981); *Continental Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991); *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 U.S.P.Q. 2d 1565 (Fed. Cir. 1995). In other words, each and every time Gross is practiced, the methods *must* deliver the drug into the intradermal compartment so that the claimed PK profile is achieved. As shown by the Pettis Declaration and Example V of the instant specification, injection into the intradermal space does not inevitably result in a PK profile having a higher C_{max} and shorter T_{max}, as required by the claims. (Pettis Decl., ¶ 9, and instant specification, ¶ [0073]). Since Gross would not *inevitably* lead to the PK profile claimed, inherent anticipation cannot be found, and the rejection should be withdrawn.

There is no evidence on this record that practicing the methods of Gross would inherently result in delivering a drug having the PK profile claimed. Moreover, the evidence provided herewith shows that the claimed PK profile would not inevitably result from practicing the prior art. In the event the Examiner disagrees, and to the extent that any rejection is based on facts within his personal knowledge, applicants request that the Examiner provide an affidavit pursuant to the provisions of 37 CFR § 1.104(d)(2).

2. THE CLAIMED INVENTION IS NOT OBVIOUS OVER GROSS IN VIEW OF PURI OR D'ANTONIO

Claims 33-52 are rejected under 35 U.S.C. §103(a) as obvious over Gross in view of Puri *et al.*, 2000, *Vaccine*, 18: 2600-12 ("Puri"), or U.S. Patent No. 6,056,716 to D'Antonio

("D'Antonio") and in further view of US Patent No. 3,814,097 to Ganderton *et al.* ("Ganderton"), and Autret et al., 1991, Therapie; 46:5-8 ("Autret").

The Examiner contends that to the extent Gross does not inherently achieve the claimed pharmacokinetic profile -- this missing element is supplied by Puri or D'Antonio. The obviousness rejection is based on the mistaken assertion that "Puri and D'Antonio disclose that intradermal injections give much greater C_{max} values than subcutaneous" (Office Action, p.4). The premise for this rejection is incorrect, and the rejection should be withdrawn.

Puri, which deals with vaccine delivery (not drugs) is concerned with the body's immune response to the vaccine -- in other words, how much antibody the body makes in response to vaccination -- not systemic distribution profiles, and certainly not C_{max} levels of the administered vaccine. To illustrate the point, at pp. 2609 - 2610, Puri describes an enhanced *immune response* -- as measured by a higher antibody response -- not an enhanced C_{max} and AUC of the vaccine substance as the Examiner contends.

D'Antonio relates to jet injection of vaccines and other substances -- not the intradermal delivery of drugs as claimed. Notably, at col. 29, line 3, D'Antonio expressly states that the entire discussion (of the D'Antonio patent) focused on *intramuscular injection.* The remainder of that paragraph discusses the possibility of administering vaccines -- *not drugs* -- into the dermis, so that less antigen could be used to generate "an increasingly rapid and effective pick-up by the immune system" (D'Antonio, col. 29, ll. 23-26).

Unlike drugs, the efficacy and potency of vaccines are not evaluated using PK studies. By contrast, the efficacy of vaccines is typically evaluated by measuring their ability to confer a protective immunity in the host. Methods for assaying potency of immunogenic compositions such as vaccines include serologic testing such as measurement of antibody titers induced against the particular antigen. For example in Puri, an ELISA assay was

developed to quantify antibody levels (not the injected vaccines) in the sera of immunized mice. Similarly, D'Antonio makes reference, not to a PK profile, but rather to a more rapid and effective pickup by the immune system. Thus, there would be no motivation either in the references themselves or in the knowledge of one of ordinary skill in the art to combine the disclosure of Gross, which relates to drug delivery, with the disclosures of Puri and/or D'Antonio, which relate to vaccine delivery. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is a suggestion found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *MPEP § 2143.01.*

The Examiner has improperly attributed parameters and properties of the drug delivery art to the vaccine art. Pharmacokinetic studies are meaningless in the vaccine art as practitioners in this field do not gauge the potency of the vaccine by its ability to be circulated systemically. In fact, as evidenced by the World Health Organization Guideline on Non-Clinical Evaluation of vaccine, pharmacokinetic studies, *e.g.*, determining serum or tissue concentrations of the vaccine are normally not needed and in fact shed no light on the efficacy of a vaccine. Thus, neither Puri nor D'Antonio supply the pharmacokinetic profile element missing from Gross; therefore, the combination does not render the claims obvious.

The Examiner relies on Ganderton for the purported teaching that multiple needle arrays result in facilitating the distribution of delivered drug to a patient. The Examiner posits that it would have been obvious to use the methods disclosed by Gross, Puri, and D'Antonio, to use the device of Ganderton.

As already described, the combination of Gross and Puri/D'Antonio fails to satisfy the legal standard for an obviousness rejection. Ganderton does not cure the deficiency of such combination. Ganderton does not describe an intradermal delivery system which is the subject matter of the instant invention. In fact, Ganderton relates to a disclosure of a multiple

needle array technology, which at best targets the outer layer of the skin, the stratum corneum, not the intradermal space, and is prone to inconsistent and irreproducible delivery. The failure of the Ganderton based technology to provide an effective delivery is, in part, due to the inability of closely spaced needles to apply enough pressure to the surface of the skin, except for, at best, puncturing the outer layer of the skin, the stratum corneum. In Ganderton's system since there are multiple fibers, the force applied to any one fiber is reduced, resulting in a low force per unit area and at best a puncturing of the outer skin surface, without achieving penetration of any of the fibers into deeper layers of the skin, much less the intradermal space. The multiple fiber pad of Ganderton thus is distinguishable from the intradermal delivery system of the instant invention because at best it achieves topical delivery through a punctured stratum corneum.

The Examiner relies on Autret for the purported teaching that intradermal delivery of a hormone results in a pharmacokinetic profile similar to subcutaneous delivery. The Examiner posits that it would have been obvious to modify the methods disclosed by Gross, Puri, and D'Antonio, with hormone delivery disclosed by Autret, to achieve similar pharmacokinetic profiles via intradermal and subcutaneous delivery. As already described, the combination of Gross, Puri, and D'Antonio fails to satisfy the legal standard for an obviousness rejection, and Autret fails to cure the deficiency of such a combination.

Autret does not describe an intradermal delivery system which is the subject matter of the instant invention. As set out in the specification as filed (*see* ¶ [0007] of the instant specification), although Autret alleges intradermal delivery of calcitonin, the length of the needle and the angle at which the needle was used for drug administration would have resulted in either subcutaneous delivery or, at best, delivery into the reticular dermis where the substance would either be slowly absorbed or diffuse into the subcutaneous region, which would be the functional equivalent of subcutaneous administration and absorption. Thus, the

method for hormone delivery taught in Autret results in subcutaneous delivery of the substance, which explains the similar pharmacokinetic profile between subcutaneous administration and reported intradermal delivery, as opposed to the improved pharmacokinetic parameters required by the claimed invention.

Thus, skilled artisans concerned with drug administration via an intradermal delivery system, would not apply or combine the disclosure in Puri/D'Antonio and Ganderton and Autret with those in Gross. Moreover, the references must be viewed without the benefit of hindsight vision afforded by Applicants' claimed invention. *M.P.E.P. § 2141.* Absent a suggestion for the teaching that PK parameters can be altered and enhanced by intradermal injection relative to subcutaneous injection, the rejection cannot stand. Thus the rejections of claims 33-52 under 35 U.S.C. §103(a) should be withdrawn.

3. CONCLUSION

The Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

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